FLG gene

filaggrin

Normal Function

The *FLG* gene provides instructions for making a large protein called profilaggrin, which is found in cells that make up the outermost layer of skin (the epidermis). Profilaggrin is cut (cleaved) to produce multiple copies of the filaggrin protein, which is involved in creating the structure of the outermost skin cells. The profilaggrin molecule can contain 10, 11, or 12 copies of the filaggrin protein, depending on the genetics of the individual. Further processing of the filaggrin protein produces other molecules that play a role in hydration of the skin.

The epidermis acts as a barrier to help minimize water loss and protect the body from foreign substances, including toxins, bacteria, and substances that can cause allergic reactions (allergens), such as pollen and dust. Filaggrin plays an important role in the skin's barrier function. It brings together structural proteins in the outermost skin cells to form tight bundles, flattening and strengthening the cells to create a strong barrier. In addition, processing of filaggrin proteins leads to production of molecules that are part of the skin's "natural moisturizing factor," which helps maintain hydration of the skin. These molecules also maintain the correct acid level (pH) of the skin, which is another important aspect of the barrier.

Health Conditions Related to Genetic Changes

atopic dermatitis

Mutations in the *FLG* gene are strongly associated with a skin disorder called atopic dermatitis (also known as atopic eczema). This condition is characterized by dry, itchy skin and red rashes. Twenty to 30 percent of people with atopic dermatitis have an *FLG* gene mutation compared with 8 to 10 percent of the general population without atopic dermatitis. Having a mutation in this gene only increases the risk of developing atopic dermatitis. Not everyone with an *FLG* gene mutation will develop the disorder. Other genes and environmental factors contribute to atopic dermatitis. Individuals with a mutation in both copies of the *FLG* gene are at greater risk of developing atopic dermatitis than those with a mutation in only one copy of the gene. The condition is typically more severe in people with two mutated copies.

In addition to *FLG* gene mutations, the number of filaggrin proteins produced from each profilaggrin molecule is associated with development of atopic dermatitis; individuals with genetic instructions for only 10 copies are at greater risk of developing the disorder than those with 11 or 12 copies.

Approximately 36 mutations in the *FLG* gene have been identified in people with atopic dermatitis. These mutations lead to production of an abnormally short profilaggrin molecule that cannot be cleaved to produce filaggrin proteins. The resulting shortage of filaggrin can impair the barrier function of the skin. Further, a lack of filaggrin leads to a shortage of natural moisturizing factor, which allows excess water to be lost through the skin and causes dry skin in affected individuals.

Research shows that the impairment of the skin's barrier function caused by a shortage of filaggrin contributes to development of allergic disorders. An allergic reaction occurs when the body mistakenly recognizes a harmless substance, such as pollen, as a danger and stimulates an immune response to it. Research suggests that without a properly functioning barrier, allergens are able to get into the body through the skin. For unknown reasons, in susceptible individuals the body reacts as if the allergen is harmful and produces immune proteins called IgE antibodies specific to the allergen. Upon later encounters with the allergen, IgE antibodies recognize it, which stimulates an immune response, causing the symptoms of allergies, such as itchy, watery eyes or breathing difficulty. Although atopic dermatitis is not initially caused by an allergic reaction, flare-ups of the rashes can be triggered by allergens. In addition, people with atopic dermatitis have an increased likelihood of developing other allergic disorders, including asthma, hay fever, and food allergies. (The tendency to develop allergic disorders is known as atopy.)

other disorders

More than 40 *FLG* gene mutations have been found to cause a common skin disorder called ichthyosis vulgaris, which is characterized by dry, scaly skin, particularly during the winter when humidity in the air is low. Affected individuals can also have unusually prominent creases on the palms of their hands and soles of their feet (palmar and plantar hyperlinearity) and an increased risk of allergic disorders, including atopic dermatitis (described above). Typically, individuals with a mutation in one copy of the *FLG* gene are mildly affected; they may have symptoms only seasonally, or they may never have obvious skin problems. Individuals with two mutated copies of the gene have more severe symptoms that may be present year-round.

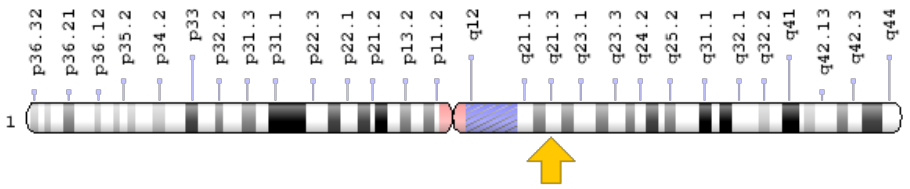
Some of the mutations associated with atopic dermatitis are also found in people with ichthyosis vulgaris. As in atopic dermatitis, the mutations lead to production of an abnormally short profilaggrin molecule that cannot be cleaved to produce filaggrin proteins. A lack of filaggrin and the molecules produced from its processing lead to the dry, scaly skin characteristic of ichthyosis vulgaris. Impairment of the skin's barrier function likely contributes to the development of allergic diseases in some people with ichthyosis vulgaris. Individuals with *FLG* gene mutations have an increased risk of developing asthma, but only if they also have atopic dermatitis. *FLG* gene mutations also increase the risk of hay fever, food allergies, and skin sensitivity to nickel, regardless of whether the person has atopic dermatitis. Additional factors,

such as owning a cat and smoking tobacco products, may increase the risk of atopic dermatitis and asthma, respectively, in people with ichthyosis vulgaris.

Chromosomal Location

Cytogenetic Location: 1q21.3, which is the long (q) arm of chromosome 1 at position 21.3

Molecular Location: base pairs 152,302,175 to 152,325,203 on chromosome 1 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- ATOD2
- epidermal filaggrin

Additional Information & Resources

Educational Resources

- Immunobiology:The Immune System in Health and Disease (fifth edition, 2001): Effector Mechanisms in Allergic Reactions
  https://www.ncbi.nlm.nih.gov/books/NBK27112/
- Immunobiology:The Immune System in Health and Disease (fifth edition, 2001): The Production of IgE
  https://www.ncbi.nlm.nih.gov/books/NBK27117/

Genetic Testing Registry

- GTR: Genetic tests for FLG
  https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2312%5Bgeneid%5D

Scientific articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28FLG%5BTI%5D%29+OR+%28filaggrin%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- FILAGGRIN
  http://omim.org/entry/135940
- ICHTHYOSIS VULGARIS
  http://omim.org/entry/146700

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_FLG.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=FLG%5Bgene%5D
- HGNC Gene Family: EF-hand domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/863
- HGNC Gene Family: S100 fused type protein family
  http://www.genenames.org/cgi-bin/genefamilies/set/1350
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=3748
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/2312
- UniProt
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